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Vitamin D Supplementation in Submariners

by

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Vitamin D is primarily recognized for its role in calcium homeostasis. However, recent research has suggested that the functions of vitamin D may be more numerous and complex. This paper is a review of basic physiology of vitamin D, recent research, and how it applies to submarine crews. Epidemiological and cellular research indicate that vitamin D may play a role in autoimmune disorders and cancer formation. These studies are not conclusive since there is a lack of well-controlled, randomized studies in humans. However, it has been established by previous studies that submariners do not receive adequate vitamin D levels from solar radiation or diet. Oral supplementation of 1,000 IU per day of vitamin D_2 is recommended based upon insufficiency observed in the past and known and possible adverse outcomes associated with insufficient vitamin D levels.

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INTRODUCTION

In recent years, vitamin D (vit D) has become the topic of many scientific articles. Although it has been recognized for over a century that vit D deficiency is detrimental,[1] many additional consequences are being identified only now. While the scientific community continues to debate about the method by which vit D should be obtained,[2-5] the US Navy should consider action to counter the health risks of vit D deficiency in the submariner population. Submariners have been singled out in previous papers external to the military as requiring extra dietary supplementation due to deficient vit D levels.[6,7]

The goal of this paper is to provide information regarding implementation of vit D supplementation for all submariners, a population at risk for vit D deficiency. Basic understanding of vit D physiology, definitions of insufficiency, deficiency, and toxicity, and possible solutions will be described using references to scientific papers. This review should provide an appreciable understanding of basic vit D physiology and assist readers in independently interpreting other scientific literature regarding this topic. Furthermore, vit D supplementation for submariners should be seriously considered based upon available data.

DISCUSSION

Vit D is a term that usually refers to the prohormones pre-vitamin D_3 (vit D_3) or pre-vitamin D_2 (vit D_2) that are both acquired from the environment, but has also been used to refer to any of the metabolites of these substances as well. The active form is 1,25-dihydroxy vitamin D [1,25-$(OH)_2$ vit D] that is produced after processing through the kidney and liver.

Basic Metabolism

Since vit D is processed through multiple forms in the body and there are many different names for each form, a summary of basic physiology is necessary before arriving at a clear understanding. To begin, vit D is ultimately acquired from one of two origins in the human body.

One form, produced in the skin as a result of exposure to sunlight, is vit D_3 and is also known as cholecalciferol. This is a result of the reaction between 7-dehydrocholesterol in the epidermis and ultraviolet radiation in the wavelengths of 290-320nm.[8,9] Overproduction of vit D_3 by this reaction is limited by increasingly synthesizing other inactive metabolites as more vit D_3 is produced which prevents toxicity.[10]

The second precursor of vit D is obtained through the diet. This is typically in the form of ingested vit D_2, also known as ergocalciferol, but can also be in the form of ingested vit D_3.[11] Although both dietary forms have been shown to prevent deficiency without adequate UV exposure,[11,12] some studies comparing the two suggest that vit D_3 supplementation may be more effective, particularly when single, large, monthly doses are used.[13,14] Many typical food sources are fortified artificially with vit D as it only naturally occurs in a few specific foods, most notably fatty fish such as salmon and herring. Fortified foods vary widely, but milk, cereal, eggs, and cheese are typically fortified.

Regardless of the source, both pre-vitamin D forms must undergo hydroxylation reactions first in the liver, then in the kidney before becoming active vit D. After initial hydroxylation in the liver, it becomes calcidiol or 25-hydroxyvitamin D [25-(OH) vit D]. Only after a second hydroxylation reaction in the kidney is active vit D formed [1,25-$(OH)_2$ vit D], also known as calcitriol.[15] This last step in the process is a finely controlled process that results in low levels and little variation in the concentration of 1,25-$(OH)_2$ vit D. Serum 25-(OH) vit D concentration is usually regarded as the marker of choice for most investigations into vit D since it is easily measured, has a long half-life in circulation (about 2-3 weeks), and correlates with clinical disease.[8,16,17]

Physiologic Activity

The most widely recognized function of vit D is to maintain calcium and phosphate at levels sufficient to support osteoblast activity.[18,19] It acts on the bones to regulate osteoblast activity, on the kidney to prevent urinary calcium excretion, and on the gastrointestinal system to increase uptake of dietary calcium.[20] Calcium is obtained by

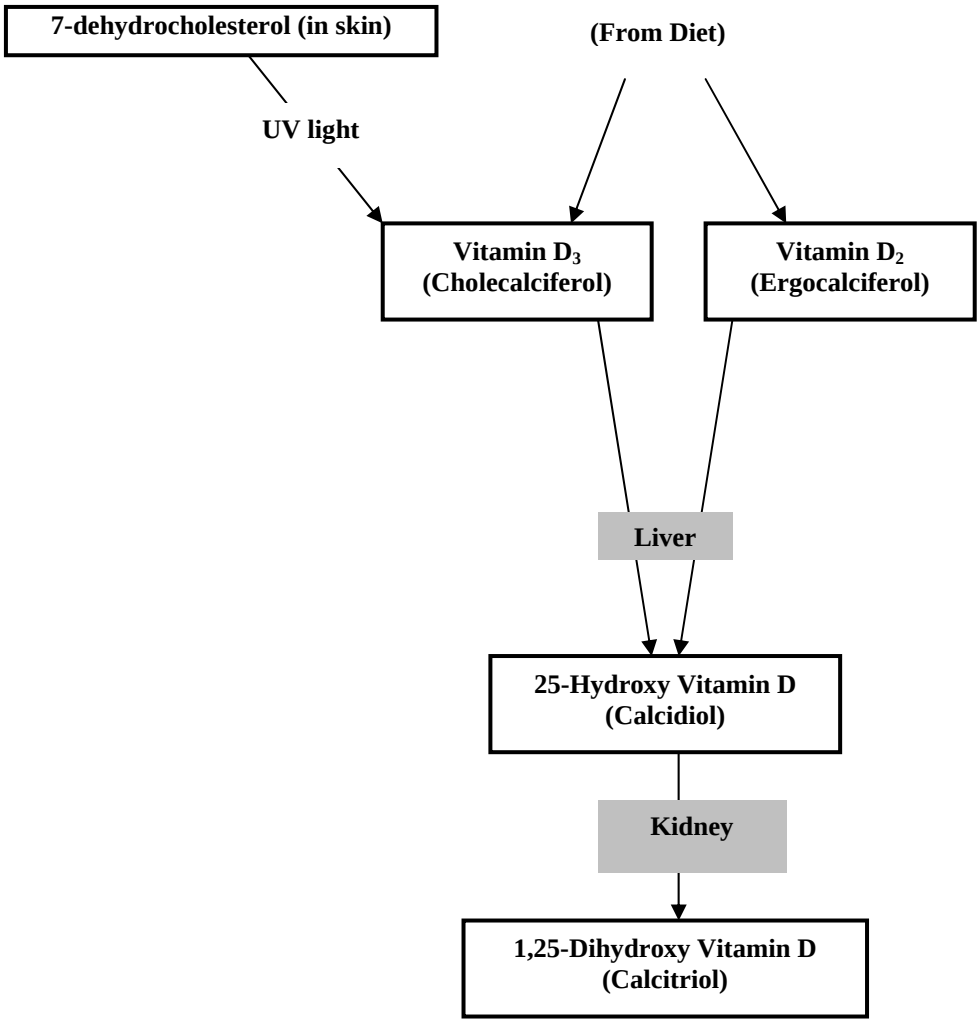

Figure 1 summarizes the primary pathways of vitamin D generation. There are many precursors to the final, active form of vitamin D although calcidiol is the form typically measured for vitamin D status.

diet primarily through vit D dependent absorption in the intestine, but also independent of vit D in a passive manner in minor amounts.[21] It is well accepted that insufficient levels of calcium result in inadequate bone mineralization with severe vit D deficiency producing rickets (in children) or osteomalacia (in adults).

In response to low calcium levels, the body will elevate parathyroid hormone(PTH) levels which will raise serum calcium and phosphate levels by breaking down existing bone matrix. The excess phosphorus is then excreted via the urinary system.[22,23] For this reason, serum PTH, calcium, and phosphorus are sometimes utilized in studies measuring vit D. Since osteoblasts utilize osteocalcin and bone-specific alkaline phosphatase, these can be used as markers for bone metabolism. There are some urinary markers that can track the excreted products of bone resorption, but because these typically require a 24-hour collection, they are rarely utilized.

In addition to the "classic" function of vit D described above, recent work has identified many more sites that are reactive to vit D. Actions of vit D on tissues are mediated by a nuclear receptor, which is the only nuclear protein in the body that binds with vit D at high affinity.[24] This vitamin D receptor (VDR) is found in tissues throughout the body to include brain, skeletal muscle, breast, prostate, colon, activated lymphocytes, macrophages, epidermal keratinocytes, and dermal fibroblasts.[17,18,25-29] It is this ubiquitous presence of the VDR throughout most body tissues that has prompted further investigations into vit D associations with disease other than those directly regarding calcium homeostasis.

Associated Disease States

Rickets is a formerly common, serious disease caused by vit D deficiency in children, but the focus of this paper is on adults. Osteomalacia is a disease mentioned above found in adults who have inadequate levels of vit D. This is a disease that can be asymptomatic for years, but can also cause vague, diffuse bone and muscle pain, muscle weakness, pelvic deformities, and waddling gait.[23,25,30] Further muscular effects were observed when studies investigating fracture reduction with the use of vit D supplementation found fracture reductions in the test group despite a lack of bone mineral density increase.[15] The explanation for this was that vit D actually prevented fractures by reducing the number of falls in the population, an assertion supported by other studies that demonstrated improved muscle strength with decreased body sway.[25,31] This was noted to be the case particularly when vit D and calcium were supplemented together.[32]

A randomized trial concluded that a combination of calcium and vit D supplementation may also play some role in colorectal carcinogenesis.[33] There is a lack of other controlled studies in this area, but there is a preponderance of evidence in many observational, epidemiological studies that seem to relate increased solar exposure (and concomitant vit D production) with decreasing rates of breast, colon, and prostate cancers.[33-41] These studies have many limitations as they are retrospective, observational studies and subject to many confounders, but may suggest some long-term effects.[7] Many studies have found no link between acute vit D levels and these cancers,[33,41-44] but these studies would fail to find any effects of long-term deficiencies in any case since they are chronologically limited. Epithelial-derived cancers seem to be suppressed in the presence of elevated vit D levels[33-35,37-43] and when human cancer cell lines are exposed to vit D it seems to be antiproliferative, induce apoptosis, promote cell differentiation, inhibit telomerase expression, and suppress tumor-induced anigiogenesis.[33,34,41,45] Thus far, there is no conclusive evidence from a controlled study to recommend vit D for cancer prevention in isolation as most work in this arena has been at the cellular level, focused on a few, limited factors, or based on observational data. However there are some authors that have concluded that, based upon overwhelming epidemiological data alone, routine solar exposure and the associated skin malignancies are an acceptable risk when faced with vit D deficiency as the alternative.[5] Currently, controlled studies are underway to further evaluate the relationship between cancer prevention and long-term vit D status, but could take many years before they are completed.[46]

Another arena of prevention currently under study is the role of vit D in autoimmune

disease. VDRs are located on monocytes and lymphocytes[47] and seem to promote self-tolerance which is the ability of the immune system to not attack host tissues.[48,49] Supplementing vit D_3 in mouse models reduced Th1-mediated disease including diabetes mellitus type 1, rheumatoid arthritis, experimental autoimmune encephalomyelitis, inflammatory bowel disease, and systemic lupus erythematosos.[47,49] In these cases, both calcium and vit D supplementation were used.[47,49,50] Several human studies regarding vit D supplementation in children demonstrated a relative risk reduction for diabetes mellitus type 1.[51-54] A recent paper details the possible associations between vit D deficiency and cancer, psoriasis, multiple sclerosis, and type 1 diabetes.[55] However, these studies are limited in the same way as the cancer studies described above. Currently, there is no conclusive evidence from a well-controlled study that supports the action of vit D for autoimmune disease prevention.

Vitamin D Deficiency and Insufficiency

There is no agreement on what serum levels of 25-(OH) vit D constitute sufficiency. Since the "primary" function of vit D is calcium regulation, some definitions have designated levels associated with these measurements. Other definitions specifically associate levels with disease states, and designate any levels above this threshold as sufficient. In order to rectify these conflicting definitions, the term "deficiency" is typically used to denote levels at which acute disease can be observed. The term "insufficiency" is used in cases where there is no clinical disease, but PTH levels can be suppressed with vit D supplementation.[25]

The 25-(OH) vit D levels that determine deficiency are those below 20-25 nmol/L (nmol/L can be approximated to ng/mL by dividing the original measurement by 2.5). At these levels, acute osteomalacia is present and PTH hormone is notably elevated. The range between what is deficient and sufficient (i.e. insufficiency) is poorly defined. The main problem is that this range is highly dependent upon calcium consumption. Since the main drive of vit D is calcium homeostasis with calcium being absorbed through the intestine, high levels of dietary calcium may overcome lower levels of vit D. Thus, elevated dietary intake of calcium may compensate for low vit D levels and allow for calcium homeostasis in an individual who would appear to be insufficient based upon 25-(OH) vit D levels alone. The threshold for insufficiency has been measured to be between 30-100 nmol/L[21,56-60] in different studies. In areas where the diet is extremely poor in calcium, vit D levels may appear sufficient, but the individual will have rickets.[61] In cases such as these, calcium supplementation alone will correct the disease.

Vitamin D Toxicity

While most of this paper is dedicated to discussing vit D deficiency, any efforts to supplement vit D must consider the risks of vit D toxicity. The symptoms of this are a result of excessive calcium. There will be increased calcium excretion in the urine with associated polyuria, weakness, lethargy, headaches, and nausea. Eventually ectopic calcifications may occur along with mental status changes, confusion, stupor, and coma.[20] As mentioned above, the body displays very tight control over 1,25-$(OH)_2$ vit D levels. Only when there are enormous amounts of the reserve form, 25-(OH) vit D, in excess of 140 nmol/L, do symptoms begin to appear.[6]

Populations at Risk

Populations at risk for vit D deficiency are those that lack both UV exposure and dietary uptake of vit D, the two sources in humans. The elderly represent a population at risk since less 7-dehydrocholesterol is contained in the epidermis to facilitate solar production of vit D_3,[62] their kidneys hydroxylate less 25-(OH) vit D to the active form, and their intestinal uptake is also decreased.[63,64] People with dark skin pigment will produce less vit D from solar exposure since the melanin absorbs some of the UV energy required to manufacture vit D_3.[65] At higher latitudes, such as New York, winter sunlight is practically incapable of producing cutaneous vit D due to the decreased angle of the sun rays, shorter daylight exposures, protective clothing for the cold, and decreased time spent outdoors.[34] Last of all, groups that minimize regular sun exposure are at risk. Groups that practice sun avoidance or wear concealing garments may also become vit D deficient despite sun exposure.[31,66]

Groups that practice sun avoidance with typical American diets have demonstrated vit D deficiency. Although it is not voluntary sun avoidance, medical residents working indoors for long hours every day have demonstrated vit D deficiency.[67] Submariners would seem similar to this group of individuals. Especially when one considers the lack of exposure to sunlight while underway coupled with insufficient winter sunlight in the ports of Groton and Bremerton. For these submariners, it is likely that dietary vit D is practically the only source of vit D for most of the year.

Previous Work with Submariners

Previous research targeting vit D deficiency in submariners has shown evidence of insufficiency. One study demonstrated a drop in mean 25-(OH) vit D levels from 31 ng/mL to 19 ng/mL over a 68 day patrol cycle. Another important aspect of this study was that PTH increased over the same period from 22 pg/mL to 30 pg/mL indicating a probable reaction to low 25-(OH) vit D levels which would indicate a vit D insufficient status. As expected, 1,25-$(OH)_2$ vit D levels remained stable throughout this study.[68] A second study looking solely at mean 25-(OH) vit D levels demonstrated a drop from approximately 23 ng/ml to 15 ng/mL over a two month deployment in non-supplemented subjects.[69] Both of these papers make recommendations for supplementing the submariner diet with vit D based upon the levels observed.

A more recent study looking at multiple parameters found a drop from 28.3 ng/mL to 22.8 ng/mL in submariners supplemented daily with 400-IU of oral vit D_2. This drop occurred after a 76-day deployment with a mid-patrol 6-day port visit in Hawaii where subjects were exposed to tropical sunlight.[70] This study experienced multiple confounders due to the interrupted deployment where subjects were allowed exposure to sunlight, procedural problems during the experiment, and large coefficients of variation. Additionally, the diets of individuals were not closely tracked making it impossible to know how much dietary vit D the individuals were getting aside from the test dose.

Vitamin D Supplementation and Renal Stones

One of the major concerns with vit D or calcium supplementation is that an increase in nephrolithiasis or kidney stones may result. This is of particular concern since renal stones are disqualifying for submariners and a majority of renal stones contain calcium. Thus, a brief review of nephrolithiasis is warranted to assuage anxiety related to this topic.

Nephrolithiasis is a fairly common condition and has a lifetime prevalence of over 10% in men.[71] Most stones are composed of calcium oxalate or calcium phosphate.[72] It is the composition of these stones that often leads to fear over vit D or calcium supplementation. However, renal stone formation is not a straightforward process. Hypercalciuria does occur in up to one-half of idiopathic stone formers and is usually as a result of a combination of three factors: (1)increased absorption through the intestine, (2)increased resorption of bone, and (3)deficient calcium resorption in the kidney.[73,74] Elevated 1,25-$(OH)_2$ vit D has resulted in increased excretion, but this is rare as this hormone is typically tightly controlled and the calcium excretion is likely caused by unreleated factors beyond the scope of this paper.[72,75,76] As mentioned above, hypercalciuria would be a sign of vit D toxicity if it were not attributable to some other cause so this would be a clear sign of over-supplementation that must be avoided. The other two factors associated with hypercalciuria would be caused by other diseases' states, such as hyperparathyroidism.

Another risk factor for stone formation is hyperoxaluria, which is simply oxalates in the urine that combine with calcium to form calcium oxalate stones.[77] One of the major factors that reduce hyperoxaluria is calcium in the diet. The calcium in the intestinal lumen forms insoluble calcium salts with the oxalates and is not absorbed. A diet low in calcium will allow more oxalates to be absorbed and subsequently excreted. Thus, a reduction in calcium in the diet may actually precipitate calcium oxalate stone formation in the kidneys by causing breakdown of bone matrix calcium in response to low serum calcium and increased oxalate excretion secondary to increased uptake in the intestine. It is for this reason that low calcium diets are never recommended for individuals with calcium stones.[78]

These recommendations are supported by several studies that have found that increasing dietary calcium results in fewer stones. A study among nurses found that increasing dietary calcium resulted in a relative risk of 0.65 for nephrolithiasis in the highest quintile compared to the lowest quintile of calcium intake.[79] A study found similar reductions in stone formation for men with increased dietary calcium under the age of 60, but not in older men.[80] Calcium supplements have sometimes been associated with an increase in stones, but this may be attributed to unpaired oxalate in the intestine since the pills are usually not taken in association with meals, so the augmented dietary calcium is not present to bind the oxalate and prevent absorption.

Other factors that are firmly established to predispose to stone formation that are widely prevalent onboard submarines include obesity, low fluid intake with associated decreased urine volume, high intake of sodium, and fad high protein diets. The presence of these

known, modifiable risk factors for renal stone formation tend to overshadow the threat of renal stone formation from vit D.

Methods of Supplementation

It is impractical to assume that submariners should be supplementing their vit D with solar exposures when in port. Vit D production from sunlight is highly dependent upon location and time of year, and a poor recommendation as any solar exposure that results in vit D production is also carcinogenic as well.[81-85] Additionally, populations that undergo shifts from little or no sunlight to sudden, intense exposures possess the highest risk of developing malignant melanoma, one of the deadliest forms of skin cancer. Although it is not entirely understood, this intermittent solar exposure results in a higher risk for malignant melanoma than those groups that are constantly outside and accrue excessive, constant exposure over many years.[86]

If solar exposure is excluded, supplementation can occur via diet. Some of the foods onboard submarines are already vit D supplemented, however whether or not any of these foods are ingested by a particular crew member is highly variable. Additionally, fresh milk, fruits, and vegetables rich in vit D are only available for the first few weeks of a deployment and consumption of these products may decrease or stop entirely after fresh stores are depleted.[68] Thus, regular meals cannot be expected to provide adequate vit D supplementation for every individual onboard a submarine. Additional oral supplementation is required to ensure minimal levels of vit D are maintained.

The level of oral supplementation is a much debated topic. As discussed in the section on renal stones, excessive vit D may lead to hypercalciuria and subsequent renal stone formation. Vit D ingested at levels of 4000 IU/day did not affect serum or urine calcium levels.[87] A recent study has shown that limiting total vit D ingestion to less than 10,000 IU/day will maintain serum 25-(OH) vit D levels below 140 nmol/L, which will prevent hypercalcuria.[6] These levels far exceed the current recommendation of 200 IU/day for children and young adults under 50 years old, [88] but have been shown to be quite safe with regard to hypercalcuria. Oral supplmentation could come in the form of a pill to be taken with meals or by fortifying food products with vit D. The problem with food fortification is that there is no way to ensure that every individual chooses to eat a particular food item. The pill is obviously not as an attractive option as food fortification, but it does ensure that everyone gets their dose.

There are several studies detailing effectiveness of a single, large, monthly vit D dose in the ranges of 50,000 IU doses.[89-91] This approach would certainly encourage improved compliance for submariners with monthly dosing as opposed to daily doses. However, the side effects of this method are unclear. Most of these studies were done in elderly populations, included small numbers of individuals, and only measured outcomes related to serum levels or morbidity, such as fracture. There were no cases of 1,25-$(OH)_2$ vit D levels high enough to be associated with hypercalcuria or obvious vit D toxicity. However, in a young population with varying amounts of vit D supplementation via diet, the safe threshold may be exceeded. There is currently no evidence available in a comparative population to recommend this approach in submariners. It was also

mentioned above that for monthly dosing, oral vit D_3 seems to be more effective at maintaining adequate levels over time than oral vit D_2.[14] However, vit D_3 is also more expensive which significantly reduces cost-effectiveness.

The cost of a single 400 IU vit D_2 pill from the Naval Branch Health Clinic in Groton, CT is listed as $0.02.[92] If supplementation is pursued, then the requested dosage could be ordered and the cost driven down due to bulk ordering. The reliability of the dose must be verified, as some vitamin supplements have been shown to have a significant problem with consistency.

Further Research

It would be possible to enlighten some of the debate in the scientific community regarding chronic vit D deficiency by utilizing studies on the health of both current and retired submariners. Many of the epidemiological studies mentioned above are based on variations in latitude to account for decreases in sun exposure and concomitant vit D production. Submariners are fairly similar individuals that have undergone intermittent periods of solar deprivation, particularly among the ballistic missile submarine crews. This is a fairly unique population that may offer unmatched opportunities to answer some basic questions regarding vit D.

One interesting project would be to evaluate submariners in their retirement. As a group, comparisons of prevalence of autoimmune disease, cancers, and osteopenia and osteoporosis could be made to known prevalence in age-matched populations. This may provide some answers regarding long-term, asymptomatic, low levels of vit D. Another project would be to measure bone mineral density in retiring or active duty submariners to see if they fall outside the expected ranges for their ages. These two studies alone could address fundamental questions that would be hard to evaluate outside a very long-term, controlled, and expensive studies.

CONCLUSIONS

A preponderance of the evidence reviewed here supports a recommendation for supplementing vit D in underway submariners. Supplementation would be an appropriate response for vit D insufficiency due to lack of solar-induced production. Supplementation would be relatively inexpensive, easy, and palatable. It is possible that ongoing research will find more vit D-associated disease in the near future as other effects of vit D continue to be closely studied. Studies have also demonstrated a range of safe levels for adequate oral supplementation. A dosage of 1,000 IU vit D_2 orally per day would be well within safe limits and likely be sufficient to maintain adequate vit D levels in submariners.

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